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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER
SHUKLA, RAM R

ART UNIT	PAPER NUMBER
1632	12

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/407,402	Applicant(s) NATESN ET AL.
	Examiner Ram Shukla	Art Unit 1632

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *06 June 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-67* is/are pending in the application.

4a) Of the above claim(s) *1-38 and 52-67* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *39-51* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *4* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☒ Other: *detailed action* .

DETAILED ACTION

1. Applicants response filed 6-06-02 has been received and entered.

Election/Restrictions

Applicant's election with traverse of claims of the invention of group II (Claims 39-51) in Paper No. 11 is acknowledged. Applicant's election of a T2098L-mutant FRB domain as the species is acknowledged. The traversal is on the ground(s) that the grouping of claims 54 and 55 is not correct. This is not found persuasive because in case of claims 54 and 55 (group III), a cell has been introduced in an organism. On the other hand in group V (claims 56-59) a nucleic acid is introduced in an organism. These two processes and the organisms thus produced are not the same and therefore have been placed in two different groups. In contrary to applicants arguments that the split is arbitrary, invention groups were based on sound reasoning as supported by restriction practice described in the MPEP.

Next applicants have argued that distinction between groups II and V as discussed in the previous office action is not correct. Again, applicants arguments are not persuasive since the invention in group II is a cell, whereas the invention in group V is an organism. While the cells in group II are present in an organism, the invention of group II are directed to cells, not organisms. Regarding the issue of "unrelated" it is noted that the previous office action discussed both the relatedness of the inventions and how the inventions were not related or distinct.

Next, applicants have argued that because of the close connection of the inventions, the search will be the same or substantially same and therefore the search and consideration of the entire invention would not be undue burdensome. However, these arguments are not persuasive because although the nucleic acids of group I may be connecting all the invention, they are patentably distinct and will require separate searches and consideration as discussed in the previous office action of 1-23-02.

Next, regarding the listed species are not species of the invention, however, these arguments are not persuasive because a transcription potentiation domain is not obvious over a DNA binding domain or a stabilization domain etc. Accordingly, search for one domain will not be coextensive with the search for another one and therefore, the species election requirement is proper and maintained. The requirement is still deemed proper and is therefore made FINAL.

2. Claims 1-38 and 52-67 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in Paper No. 11.

3. It is noted that the elected claims 39 and 45 encompass the invention recited in claims 1-5 and 31 whereas claim 40 depends from claim 6. Accordingly, the invention of claims 1-5 and 31 will be examined to the extent they read on the elected invention.

4. Claims 39-51 are objected to because they are dependent on withdrawn claims.

5.

Notice To Comply With Requirements For Patent Applications Containing Nucleotide Sequence And/Or Amino Acid Sequence Disclosures.

This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 CFR 1.821 through 1.825 for the reason(s) set forth on the attached Notice To Comply With Requirements For Patent Applications Containing Nucleotide Sequence And/Or Amino Acid Sequence Disclosures.

Specifically the application fails to comply with CFR 1.821(d), which states:

(d) Where the description or claims of a patent application discuss a sequence that is set forth in the "Sequence Listing" in accordance with paragraph (c) of this section, reference must be made to the sequence by use of the sequence identifier, preceded by "SEQ ID NO: " in the text of the description or claims, even if the sequence is also embedded in the text of the description or claims of the patent application.

For example, the specification discloses nucleotide and amino acid sequences on pages 47-50, 54,55, 62-66, etc. However, these sequences are not identified by sequence identifiers in the brief description of the figures. Applicants are advised to carefully check the entire specification for any disclosed sequences and identify them with sequence identifiers.

For compliance with sequence rules, it is necessary to include the sequence in the "Sequence Listing" and identify them with SEQ ID NO. In general, any sequence that is disclosed and/or claimed as a sequence, i.e., as a string of particular bases or amino acids, and that otherwise meets the criteria of 37 CFR 1.821(a), must be set forth in the "Sequence Listing." (see MPEP 2422.03).

For the response to this office action to be complete, Applicants are required to comply with the Requirements For Patent Applications Containing Nucleotide Sequence And/Or Amino Acid Sequence Disclosures.

6. Instant application is a CIP of 08/672,132, 6/27/96, 09096732 filed 6/11/98 and 09/262,721 filed 03/04/99. However, it is unclear as to what was added to the specification of 08/672,132 which resulted in 09/096,732 or 09/262,721. Accordingly, instant application is assigned the filing date of 9/28/99.

Claim Rejections - 35 USC § 112

7. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

8. Claims 39-51 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for an in vitro method for rendering a cell capable of expressing a target gene in a cell in a ligand

dependent manner by transducing the cell with a recombinant nucleic acid that comprises a p65 domain comprising a part or all of the amino acids spanning from 361 to 550 of human NF-kB p65 and a ligand binding domain wherein the ligand binding domain is selected from VP16 B, VP16 C, HSF, CTF and progesterone receptor domain and an isolated cell comprising a target gene construct comprising the target gene and the recombinant nucleic acid, does not reasonably provide enablement for a method wherein the cell is present in vivo in an animal. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The claimed invention is directed to a method for rendering a cell capable of expressing a target gene in a cell in a ligand dpendent manner by transducing the cell with a recombinant nucleic acid that comprises a p65 domain comprising part of all of the nucleic acids spanning from 361 to 550 of human NF-kB p65 and a ligand binding domain, wherein the cell is present in vitro or is within an organism and therefore the claim encompasses a method of gene therapy and administration of the nucleic acid to a cell in an animal in vivo by any route. However, the specification as filed is not enabling for an in vivo method or for gene therapy because the a method of gene therapy was unpredictable at the time of the claimed invention and is unpredictable even today, as discussed below. It is noted that an artisan of skill would have required undue experimentation to practice the claimed invention commensurate with the full scope of the claims because the artisan would have required extensive experimentation to solve the problems and obstacles recognized in the field of gene therapy and that make the field of gene therapy unpredictable.

The specification teaches the construction of DNA plasmids encoding DNA-binding and transcription activating fusion proteins, e.g., GAL4-FRAP, FPAP-l/P16, ZF1fD1-FRAP, FRAP-p65, to create a representative final construct, pCGNN-ZFF)l-IFFB. The specification teaches the construction of a

retroviral vector, SMTN-ZFFFJ1-3FKBP. The specification teaches cell culture experiments demonstrating rapamycin-dependent transcriptional activation of reporter gene constructs using transient or stable cell transfection assays employing the DNA plasmids encoding the fusion proteins and the DNA plasmids encoding the reporter genes. The specification further demonstrates rapamycin-dependent production of hGH in nude mice by i.m. transplantation of the cells transfected with the above constructs. The specification additionally teaches cell culture assays using DNA constructs encoding hybrid transcription factors for constitutive expression of the reporter gene construct(see the 41-67 of the specification). The specification also teaches prophetic example for making a p65-GAL4-progesterone ligand binding domain, ZFHD1-p65-GAL4, rtTA-p65 and S3HP65-HSF-Sp65 expression vectors (see pages 68-70 of the specificaton). However, cell culture and nude mouse assays for regulated or constitutive levels of reporter gene expression do not provide a prediction of therapy for any disease. Applicants fail to provide a correlation to levels of expression of any particular therapeutic target gene of interest in the transfection assays of the instant application, in particular in methods of ex vivo gene transfer.

The status of the gene therapy art, in particular, at the time of the effective filing date of the claimed invention, was undeveloped and unpredictable in terms of achieving in vivo expression levels of a gene of interest. Orkin et al. (1995) support such an observation, who state "While the expectations and the promise of gene therapy are great, clinical efficacy has not been definitely demonstrated at this time in any gene therapy protocol, despite anecdotal claims of successful therapy and the initiation of more than 100 recombinant DNA Advisory Committee (KAC)-approved protocols." Significant problems remain in all basic aspects of gene therapy. Orkin et al. further report the difficulty of extrapolating from experiments in animal models to human studies, in particular with respect to the efficiency of gene delivery and the host response to viral vectors. See page 14, 4th paragraph. Orkins report therefore indicates that the art of gene therapy was

unpredictable at the time of the invention. It is noted that the unpredictability of a particular art area may alone provide reasonable doubt as to the accuracy of the broad statement made in support of enablement of claims. See Ex parte Singh 17 USPQ2d 1714 (BPAI 1991).

In the instant case, there is no evidence or reasonable correlation thereto in the specification which supports the production of levels and duration of expression of any therapeutic target gene of interest sufficient to provide treatment by means of the claimed methodology. Applicants merely demonstrate rapamycin-dependent hGH gene transfer in nude mice which can be assayed to detect minimal levels of expression. Accordingly, such a demonstration fails to provide correlative evidence of sufficient levels of expression of a target gene of interest for therapy.

Additionally, with regard to in vivo gene expression, numerous factors complicate gene therapy with respect to predictably achieving levels and duration of expression which have been shown to be overcome by routine experimentation. These include, the fate of the DNA vector itself (volume distribution, rate of clearance into the tissues, etc.), the in vivo consequences of altered gene expression and protein function, the fraction of vector taken up by the target cell population, the trafficking of the genetic material within cellular organelles, the rate of degradation of the DNA, the level of mRNA produced, the stability of the mRNA produced, the amount and stability of the protein produced, and the protein's compartmentalization within the cell, or its secretory fate, once produced. See Eck and Wilson, 1995, page 82, column 1, first paragraph. These factors differ dramatically based on the vector used, the route of administration of the vector, the protein being produced, and the disease and/or host being treated. The specification fails to provide guidance for any of the above parameters for in vivo or ex vivo gene therapy and only teaches regulated expression of a hGH target gene in nude mice by intramuscular transplantation of cells transfected with the constructs encoding the fusion transcription factors of the invention. The claims encompass any route of administration, however,

the specification specifically teaches intramuscular transplantation and fails to teach how cell-targeting may be accomplished to specific tissue or cell types using other routes of administration. For the treatment of a wide range of diseases, cell targeting and other routes of administration of the fusion constructs of the invention would be necessary, however, Applicants fail to teach or provide a reasonable correlation thereto and route of administration or cell-targeting techniques which effectively target expression of a gene of interest to any particular cell type at levels sufficient to cause a therapeutic effect. Orhin et al. clearly support that cell-targeting methodology is undeveloped at the time of the invention. Specifically, Orkin et al. discuss that cell targeting methodologies have not yet reached clinical application and that research in these areas within the context of gene therapy strategies is in its infancy (see page 8, last paragraph and paragraph bridging pages 9-10).

The claimed invention encompasses an enormous number of possible combinations and arrangements of DNA sequences encoding transcription factors or composite transcription activation domains, and target gene sequences in operable linkage with promoter sequences and DNA recognitions sequences. The prior art indicates that the creation of functional chimeric proteins containing DNA-binding domains or transcriptional activation domains is unpredictable. See, e.g., Orloff et al. (Nature, 1990), Lui et al. ammunology Today, 1993), Weintraub et al. (Science, 1991), Bergmann et al. (J. Steroid Biochem. Molec. Biol., 1994), Qi et al. (Molecular and Cellular Biology, 1995) and Sadowski et al. (Nature, 1993). Collectively, the prior art supports that transcriptional activator domains and DNA binding domains are not freely interchangeable to produce chimeric proteins that are capable of transactivation (which is required for promoting target gene expression). Furthermore, on page 57 of the specification, Applicants list chimeric transcription factors which fail to activate transcription and constitutive expression of the target marker gene in cell

culture methods of the invention, e.g., GAL4-p65 (361-450), GAL4Oct2 Q domain (aa95-I 60), GAL4-Oct2 P domain (aa43 8-479), and GAL4-EWS11 (SRSYGQQGSGS). Regarding claims 50, it is noted that the specification has described how to modify a plasmid described in US 5.654,168 for making a tet-A based expression system, however, in view of the discussion above, it is not clear whether an artisan would have been able to use such a plasmid or construct without undue experimentation. Regarding claim 51, it is reiterated that while an artisan might have been able to make such a vector, the specification fail to describe as to how an artisan have used it in view of the discussion above and the unpredictability of the art of chimeric transcription factors. The courts have stated that reasonable correlation must exist between scope of exclusive right to patent application and scope of enablement set forth in patent application. Ex parte Maizel, 27 USpQ2d 1662 (BPAI 1992). As such, Applicants provide no nexus between the DNA constructs employed in the examples and DNA constructs encoding transcriptional activation domains known in the prior art and demonstrated to be unpredictable in terms of activating transcription, or DNA constructs that have yet to be developed by trial and error experimentation by identifying and isolating cellular transcriptional activation components for the construction of recombinant DNA constructs which encode the components which may activate transcription of a target gene of interest. As such, the skilled artisan would have to partake in undue experimentation without a reasonable expectation of identifying, isolating, combining and arranging DNA constructs which encode the components essential for the activation of transcription of a target gene of interest.

In summary, the specification is not enabling for the claimed invention commensurate with the scope of the claims and therefore, limiting the scope of the claimed invention to in vitro method for rendering a cell capable of expressing a target gene in a cell in a ligand dependent manner by transducing the cell with a recombinant nucleic acid that comprises a p65 domain comprising a part or all of the amino acids spanning from 361 to 550

of human NF-kB p65 and a ligand binding domain wherein the ligand binding domain is selected from VP16 B, VP16 C, HSF, CTF and progesterone receptor domain and an isolated cell comprising a target gene construct comprising the target gene and the recombinant nucleic acid, is proper.

9. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

10. Claims 39-51 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 39 and 40 recite the term "rendering a cell capable of", however, it is unclear if the term is intended to be open or closed with respect to the metes and bounds of the claimed invention. Additionally, "capable of" only indicates potential and it is indefinite whether the phenomenon really occurs.

Claims 45, 46, 49-51 recite the term "containing", it is unclear if the term is intended to be open or closed with respect to the metes and bounds of the claimed invention. Use of the term "comprising" or "consisting" is suggested for open or closed language.

Claims 49-51 recite the term "being capable of", however, it is unclear if the term is intended to be open or closed with respect to the metes and bounds of the claimed invention. Additionally, "capable of" only indicates potential and it is indefinite whether the phenomenon really occurs.

Claim Rejections - 35 USC § 102

> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

11. Claims 39, 41, 43-45, and 47 are rejected under 35 U.S.C. 102(b) as being anticipated by Schmitz et al. (The Journal of Biological Chemistry 270:15576-15584, 1995).

Schmitz et al. teach recombinant DNA molecules encoding polypeptides comprising a DNA-binding domain of GAL4 protein and portions of human NF-KB p65 comprising residues fiom the regions 361-450 and 361-550 (pp 3808-11) Schmitz et al. also teach co-transfection of cells with said DNA molecules and a CAT reporter construct with GAL4-binding sites in the promoter region. Schmitz et al. further teach that residues 521-550 of NF-KB comprise a strong transactivating domain, TA1, and that a second transactivating domain, TA2, is present in residues 441-518 (p. 3809). It is noted that treatment of the cells with PMA further increased transcription and that the activation domain of p65 is responsive to PMA indicating ligand depend activation. Accordingly, claimed invention is anticipated by Schmitz et al.

12. Claims 39-49 are rejected under 35 U.S.C. 102(a) as being anticipated by Burcin et al (Proc. Natl. Acad. Sci. USA 96:355-360, 1999).

Burcin et al teach an transcription factor that comprises GAL4 DNA binding domain, Progesterone receptor and VP16 or p65 activation domain. The art also teaches a target gene expression vector and host cells comprising the transcription factor expressing vector and the target gene expression vector (see figures 1 and the methods section on page 355 right column continued into left column on page 356).

Accordingly, the claimed invention is anticipated by Burcin et al.

13. Claims 39-49 are rejected under 35 U.S.C. 102(a) as being anticipated by Sui et al (The Journal of Biological Chemistry 274:9449-9454, 1999).

Sui et al teaches fusion transcription factor comprising androgen receptor, activation domain of p65 and DNA binding domain of GAL-4, a target gene expression vector and cells comprising a vector expressing the transcription factor and the target gene vector (see figure 1-8) and the

methods section on page 9450). Accordingly, claimed invention is anticipated by Sui et al.

14. US Publication No: 2002/0048792, publication date 4-25-02, effective filing date 8-26-1997 and US 6,015,709, 1018-00 (from the same assignee and at least one common inventor) are made of record. It is noted that these arts disclose using two nucleic acid constructs –one comprising an activation domain and a DNA binding domain and the other comprising an activation domain and a ligand binding domain.

15. No claim is allowed.

When amending claims, applicants are advised to submit a clean version of each amended claim (without underlining and bracketing) according to § 1.121(c). For instructions, Applicants are referred to http://www.uspto.gov/web/offices/dcom/olia/aipa/index.htm.

Applicants are also requested to submit a copy of all the pending/under consideration claims.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ram R. Shukla whose telephone number is (703) 305-1677. The examiner can normally be reached on Monday through Friday from 7:30 am to 4:00 p.m. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Deborah Reynolds, can be reached on (703) 305-4051. The fax phone number for this Group is (703) 308-4242. Any inquiry of a general nature, formal matters or relating to the status of this application or proceeding should be directed to the Dianiece Jacobs whose telephone number is (703) 305-3388.

Ram R. Shukla, Ph.D.

RAM R. SHUKLA, PH.D
PATENT EXAMINER